inflammation in an organism" and under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Claims 54 and 65-71 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Angeles et al. (claim 54) and the U.S. patent (4,782,077) of de la Parra (claims 65-71). In view of the amendments herein and the reasons detailed below, Applicants request that these rejections be withdrawn and claims 53, 57, 59-60 and 63-71 be allowed to issue. Claims 54-56, 58 and 61-62 are cancelled without prejudice to the prosecution of this subject matter in separate patent applications.

Rejections under 35 U.S.C. §112, ¶1 – "Enablement"

The Examiner has rejected claims 53-64 under 35 U.S.C. §112, first paragraph, stating that the specification "does not reasonably provide enablement for a method of inhibiting mutagenesis, inhibiting fungal growth or inhibiting inflammation in an organism." The Examiner maintains that the prediction of in vivo efficacy from in vitro findings is inexact at best and thus concludes that the claims directed toward therapy in humans have not been enabled by the materials provided in the specification. Applicants respectfully disagree with the opinion of the Examiner and the reference cited in support of this position (Wickware, 1997). Applicants provide further support for their contention that such tests are in fact excellent predictors of in vivo efficacy (see below).

However, in order to further the prosecution in this case, the claims directed towards methods of treating disease (Claims 54-57), of inhibiting fungal growth in plants and animals (claim 58), and related dependent claims (claims 61-62) have been cancelled without prejudice to the prosecution of such subject matter in further continuation applications. Thus, the rejections related to these claims are now moot.

As for the remaining claims rejected under the first paragraph of 35 U.S.C. §112, claim 53 is directed to "[a] method of inhibiting mutagenesis in an organism[,]." In Example 2 provided on pages 32-35 of the specification, substantial and credible data are provided that demonstrate the inhibitory activities of at least four of the components of the organic solvent extract of Aristolochia taliscana on mutagenic activity as determined in the organism *Salmonella typhimurim* using the Ames test (see Tables 4-7). The Ames test has been widely accepted by the scientific community for many years as predictive of in vivo activity of tested compounds. As documented in both Probst et al. (Environ Mutagen 1981;3:11-32) and McCann et al. (Mutat. Res. 1988;205:183-195) (copies these articles, as well as those cited below, are attached), the Ames test is not only widely used by many governmental regulatory agencies, academic institutions and chemical companies as a direct measure of mutagenicity, but is also strongly correlated with various measures of mutagenesis/carcinogenicity in vivo, including unscheduled DNA synthesis in adult rat hepatocytes (Probst et al., 1981) and various murine cancer models including the TA100 Aroclor-induced rat S9

model (McCann et al., 1988). Thus, Applicants respectfully disagree with the Examiner's statement that the anti-mutagenic properties of the extract in vitro do not support the inhibition of mutagenesis in an organism and request that this claim and the dependent claims 59 and 60 be allowed to issue.

Similarly, the Examiner has rejected claim 57, stating "[T]he instant specification as filed has not provided adequate information regarding any effective treatments of fungal infections." In Example 5, shown on page 36 of the specification, substantial and credible data are provided that demonstrate the anti-fungal effects of at least eleven of the components of the organic solvent extract of Aristolochia taliscana as determined using three different fungal *strains (Botryis cinerea, Rhizoctonia solani* and *Saprolegnia asterophora*). While the Examiner cites the editorial comment of Wickware in support of her contention that in vitro efficacy is not predictive of in vivo efficacy, the Examiner's reliance on Wickware is directly contradicted by numerous scientific studies published prior to the priority date of the instant invention that demonstrate strong correlations between in vitro susceptibility and clinical outcome.

For example, Radetsky et al. (J. Clin. Microbiol. 1986;24:600-606) report a microtiter broth assay system for susceptibility testing of pathogenic Candida species that is strongly correlated with in vivo outcome in both laboratory animals and humans. Moreover, throughout the 1990's, in vitro susceptibility testing of fungal isolates became an increasingly important tool in the clinical management of fungal infections in individuals with compromised immune systems. Many

published studies report strong correlations between in vitro susceptibility to antifungal agents and clinical outcome (for specific examples see Cameron et al., Antimicrob. Agents Chemother. 1993;37:2449-2453 or Quereda et al., Eur. J. Clin. Microbiol. Infect. Dis. 1996;15:30-37). More recent studies have confirmed these findings in AIDS patients and extended them to non-AIDS patients (Aller AI et al., Antimicrob. Agents Chemother 2000;44:1544-1548; Walmsley S et al., Clin. Infect. Dis. 2001;32:1544-1561) and to other patient populations (Arikan et al. Clin. Infect. Dis. 1998;26:903-90; Lee SC et al., Antimicrob. Agents Chemother 2000;44:2715-2718).

In the few reported studies where the correlation between in vitro susceptibility and clinical outcome was weaker, relatively straightforward modifications, such as relating outcome to either the minimum effective concentration in vitro (Gonzalez GM et al., Antimicrob. Agents Chemother 2001;45:1854-1859) or the content of specific biochemical markers in the fungal culture (Arthington-Skaggs BA et al., Antimicrob. Agents Chemother 2000;44:2081-2085), rather than to the minimum inhibitory concentration, significantly improved the strength of the in vitro/in vivo relationship. In still other cases, a less strong correlation between in vitro and in vivo behavior was found not because the compounds failed to work in vivo, as implied by the examiner, but rather because they worked even better in vivo than would have been predicted from the in vitro studies (Huang YC et al., Am. J. Perinatol. 2001;18:141-146).

Based on the specific examples provided in the specification together with these studies and

numerous others that demonstrate the strong predictive nature of in vitro susceptibility testing in predicting clinical outcome in antifungal therapies, Applicants respectfully disagree with the Examiner's statement that the anti-fungal properties of the extract fail to enable its application as "[a] method of inhibiting fungal growth in a substrate...", as claimed in claim 58 and request that this claim and the dependent claims 63 and 64 also be allowed to issue.

Rejections under 35 U.S.C. §112, ¶2 – "Indefiniteness"

The Examiner has rejected claims 53-64 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Claims 53 and 57 have been amended as suggested by the Examiner to define the term "extract" as an extract "...having been prepared by a process which includes extracting plant material from Aristolochia taliscana with an organic solvent, such that the extract is substantially free of aristolochic acids." The Examiner also expressed some reservation regarding the use of the phrase "one or more...active compounds isolatable therefrom[.]," stating that the composition defined by this phrase was not clearly delineated. The data provided in Examples 2 and 5 in the specification clearly demonstrate beneficial aspects of a variety of specific and positively-identified compounds isolated from the crude extract (N. B. Tables 4-9). However, Applicants have removed the objected to phrases from the relevant claims (claims 53 and 57).

Applicants believe that the claims as amended clearly define the claimed invention. Applicants therefore request the withdrawal of this rejection. Claims 65 and 68 have also been amended to specify the type of Aristolochia taliscana extract claimed.

Rejections under 35 U.S.C. §102(b)

The Examiner has rejected claim 54 and claims 65-71 under 35 U.S.C. §102(b) as being anticipated by Angeles et al. and de la Parra, respectively.

As expressed in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1997), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the ... claim[.]" (*Richardson v. Suzuki Motor Co. Ltd.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920). In the present instance, for the pending claims to be anticipated, either de la Parra or Angeles et al. must teach a method for the isolation of an extract of Aristolochia taliscana that is substanitally free of aristolochic acids and which is useful in inhibiting mutagenesis and/or fungal growth.

With regard to Angeles et al and claim 54, Angeles et al. specifically examined the effects of aristolochic acid on tumor size and other parameters. Since the claims of the present invention

specifically exclude aristolochic acid, Applicants maintain that Angeles et al. does not anticipate the claims of the instant invention. Applicants therefore respectfully request that claim 54 be allowed to issue.

Regarding de la Parra (U.S. patent 4,782,077), Applicants note several substantial differences between the active ingredients disclosed therein and those of the claimed invention and the methods by which such ingredients have been isolated. In de la Parra, Aristolochia taliscana root was pulverized, suspended in hexane, and extracted using a Soxhlet extractor. The residue from this extraction was suspended in benzene, and again extracted using a Soxhlet extractor. The residue of this second extraction was resuspended in benzene:hexane (2:3) and fractionated through an alumina chromatography column using benzene:ether (7:3) as an eluant. This procedure generated a relatively pure form of the aristolactam alkaloid taliscanin, which subsequently was used in all clinical trials cited in the specification of de la Parre.

In contrast, in the instant invention, a single benzene extraction was performed on pulverized roots and rhizomes of Aristolochia taliscana, followed by fractionation, first through a Fractogel TSK HW 40 column and then through a variety of other columns to assist in the identification of various components of the extract. The results of these assays, shown in Table 3 of the specification, clearly indicate that the benzene extract claimed in the instant invention is substantially free of arisotlactams in general and taliscanin (taliscanine) in particular. Thus, with regard to both the

process by which it was obtained and its composition, the extract claimed by the Applicants is patentably distinct from that disclosed by de la Parra. Furthermore, because the process by which it was obtained is demonstrably distinct from that used by de la Parra, in re Sussman [141 F, 2d, 267, 60 U.S.P.Q. 538 (CCPA 1944)] is not relevant in this case, and the contention that the presence of eupomatanoids and/or aristolactam "are merely inherent properties of an already known composition" cannot be sustained. On this basis, de la Parra cannot anticipate the instant invention. Applicants therefore respectfully request that claims 65-71 be allowed to issue.

CONCLUSION

Based on the foregoing remarks, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 53, 57 and 65-71 have been amended as follows:

53. (Amended) A method of inhibiting mutagenesis in an organism, which method comprises administering to the organism, an effective anti-mutagenic amount of an extract from Aristolochia taliscana, said extract having been prepared by a process which includes extracting plant material from Aristolochia taliscana with an organic solvent, such that the extract is substantially free of aristolochic acids. ~~or one or more anti-mutagenically active compounds isolable therefrom.~~

57. (Amended) A method of inhibiting fungal growth in a substrate, which methods comprises administering to the substrate an effective anti-fungal amount of an extract from Aristolochia , said extract having been prepared by a process which includes extracting plant material from Aristolochia taliscana with an organic solvent, such that the extract is substantially free of aristolochic acids. ~~or one or more anti-mutagenically active compounds isolable therefrom.~~

65. (Amended) A composition comprising an extract from Aristolochia taliscana, wherein the extract has been prepared by extraction of plant material from the Aristolochia species

with an organic solvent and contains at least 10% by weight of a eupomatenoid, wherein the extract is substantially free of aristolochic acids.

68. (Amended) A composition comprising an extract from Aristolochia taliscana wherein the extract has been prepared by extraction of plant material from the Aristolochia species with an organic solvent, wherein the extract contains at least 25% by weight of a phenolic eupomatenoid compound, at least 8% of Licarin-A and at least 8% by weight of a non-phenolic eupomatenoid compound, and wherein the extract is substantially free of aristolochic acids.